# The present and future disease burden of hepatitis C virus (HCV) infection with today's treatment paradigm

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SUMMARY. The disease burden of hepatitis C virus (HCV) is expected to increase as the infected population ages. A modelling approach was used to estimate the total number of viremic infections, diagnosed, treated and new infections in 2013. In addition, the model was used to estimate the change in the total number of HCV infections, the disease progression and mortality in 2013–2030. Finally, expert panel consensus was used to capture current treatment practices in each country. Using today's treatment paradigm, the total number of HCV infections is projected to decline or remain flat in all

# INTRODUCTION

It is estimated that >185 million people were infected with the hepatitis C virus (HCV) in 2005 in the world [1]. HCV infection can lead to liver damage resulting in liver fibrosis, cirrhosis, decompensated cirrhosis and hepatocellular carcinoma (HCC) [2]. Individuals with more advanced stages of liver disease may require transplantation, and HCV remains a leading indication for liver transplants [3].

Abbreviations: G, Genotype; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IDU, injection drug use; INE, National Institute of Statistics; Peg-IFN, Pegylated interferon; PI, protease inhibitor; RBV, ribavirin; RNA, ribonucleic acid; SMR, standard mortality ratio; SVR, sustained viral response; UN, United Nations.

Correspondence: Homie A. Razavi, Center for Disease Analysis, 901 Front Street, Suite 291, Louisville, CO 80027, USA. E-mail: homie.razavi@centerforda.com †Denotes senior authors. countries studied. However, in the same time period, the number of individuals with late-stage liver disease is projected to increase. This study concluded that the current treatment rate and efficacy are not sufficient to manage the disease burden of HCV. Thus, alternative strategies are required to keep the number of HCV individuals with advanced liver disease and liver-related deaths from increasing.

*Keywords:* diagnosis, disease burden, epidemiology, HCV, hepatitis C, incidence, mortality, prevalence, treatment.

The aim of this study was to estimate the current and future impact of HCV disease burden if the current treatment paradigm and response rate continued. A model was developed to forecast HCV disease progression and the number of cases at each stage of liver disease by country.

# METHODOLOGY

## Inputs

The historical epidemiology of HCV was gathered through a literature search, analysis of unpublished data and discussion with expert panels, as described previously [4]. When no input data were available, analogues (data from countries with a similar healthcare practice and/or risk factors) or expert inputs were used. Ranges were used to capture uncertainty in inputs with wider ranges implying greater uncertainty. As shown previously [4], HCV epidemiology data were reported in different years. Therefore, a mathematical model was used to estimate the 2013 HCV-infected populations for all countries.

## Model

A disease progression model was constructed in Microsoft Excel<sup>®</sup> (Microsoft Corp., Redmond, WA) to quantify the size of the HCV-infected population, by the liver disease stages, from 1950–2030. The size and impact of the HCV-infected population prior to 1950 were considered negligible for the purposes of this analysis. The model was set up for sensitivity and Monte Carlo analysis using Crystal Ball<sup>®</sup>, an Excel<sup>®</sup> add-in by Oracle<sup>®</sup>. Beta-PERT distributions were used for all uncertain inputs. The Excel<sup>®</sup> optimization add-in, Frontline Systems' Solver, was used to calculate the number, age and gender distribution of the annual acute infections as described below.

Microsoft Excel was selected as a platform due to its transparency, availability and minimal need for operator training. The disease progression was modelled using the flow shown in Fig. 1 and calculations shown in Equation 1.

$$TotalCases_{Stage_{x}} Year_{y} AgeCohort_{z} = \left(\frac{4}{5}\right) \left(TotalCases_{Stage_{x}} Year_{y-1} AgeCohort_{z}\right) \\ + \left(\frac{1}{5}\right) \left(TotalCases_{Stage_{x}} Year_{y-1} AgeCohort_{z-1}\right) + \\ NewCases_{Stage_{x}} Year_{y} AgeCohort_{z} - \\ AllCauseMortality_{Stage_{x}} Year_{y} AgeCohort_{z} - \\ Progressed_{Stage_{x}} Year_{y} AgeCohort_{z} - Cured_{Stage_{x}} Year_{y} AgeCohort_{z} - \\ \end{cases}$$

where:

 $NewCases_{Stage_x Year_y AgeCohort_z} = (TotalCases_{Stage_{x-1} Year_{y-1} AgeCohort_z}) (ProgressionRate_{Stage_{x-1} \rightarrow Stage_x AgeCohort_z})$ 

 $BackgroundMortality_{Stage_x Year_y AgeCohort_z} = (TotalCases_{Stage_x Year_{y-1}} AgeCohort_z) (AdjustedMortalityRate_{AgeCohort_z})$ 

 $\begin{array}{l} Progressed_{Stage_x \ Year_y \ AgeCohort_z} = \\ \left( TotalCases_{Stage_{x-1} \ Year_{y-1} \ AgeCohort_z} \right) \\ \left( ProgressionRate_{Stage_x \rightarrow Stage_{x+1} \ AgeCohort_z} \right) \end{array}$ 

$$Cured_{Stage_x Year_y} = \sum_{Genotype=1}^{w} (TotalTreated_{Genotype_w Stage_x Year_y}) (AverageSVR_{Genotype_w Year_y})$$

The model started with the annual number of acute infections that progressed to chronic HCV (viremic) infection after accounting for spontaneous clearance of the virus. The progression of these new cases was followed along with all chronic infections from prior years. Unless specified, the scope of the model was limited to viremic, HCV ribonucleic acid (RNA) positive cases. Nonviremic cases (those which spontaneously cleared the virus or were treated and cured) were not considered even though they would test positive to HCV antibodies and may still progress to more advanced stages of liver disease despite viral clearance [5].

Total cases, at any stage of the disease, were calculated as described in Equation 1. The total number of cases at



Fig. 1 The flow of the HCV disease progression model.

each stage of the disease was tracked by age and gender. Five-year age cohorts were used through age 84, and those aged 85 and older were treated as one cohort. Each year, one fifth of the population in each age group, except for 85 and older, was moved to the next age cohort to simulate aging.

# Total number of HCV infections

The historical number of HCV infections, and the age and gender distribution, were gathered through a literature search and discussions with an expert panel [4]. These data were used to estimate the historical number of new HCV infections as described below. The total annual number of viremic HCV cases and the age/gender distribution were calculated by adding the total cases for every stage of the disease outlined in Fig. 1.

# New HCV infections

When available, the reported/calculated number of new infections was used. In most countries, the number of new HCV infections was not available and was back-calculated. Equation 2 describes that at any point in time, the total number of HCV infections equals the sum of all new infections minus the number of spontaneously cleared cases, all-cause and liver-related mortality and cured cases.

$$TotalHCVInfections_{Year_x} = \sum_{t=1950}^{x} (NewInfections_t - SpontaneouslyCured_t) - Mortality_t - Treated Cured_t)$$

The number of new infections was back-calculated using a two-step process that first calculated the annual number of new cases, followed by the age and gender distribution of these cases. The annual number of new cases was calculated using the known number of total HCV infections in a given year in a country. The model calculated the annual number of all-cause mortality, liver-related deaths and cured cases as described below. A spontaneous clearance rate of 18% (15–45%) was used [6–8] except as noted below.

The Excel<sup>®</sup> optimization add-in, Solver, was used to determine an average number of new infections per year, which resulted in the right- and left-hand sides of Equation 2 becoming equal. However, the annual number of new cases did not remain flat since 1950. Thus, an annual relative incidence value was used to describe the change in the number of new infections over time. Relative incidence was set to one in 1950, and a discussion with the expert panel was used to identify the years when new infections peaked using the risk factors common in the country (nosocomial infections, injection drug use,

etc). Peak years were typically in the early 1990s, prior to implementation of blood supply screening and before the potential implementation of needle exchange programmes for IDU. Discussions with the expert panel were also used to estimate any decline in relative incidence due to a reduction in risk factors, including blood screening and implementation of needle exchange programmes for IDU. A curve was fitted from 1950 to the estimated peak, and a second curve followed the decline in relative incidence. Excel<sup>®</sup> Solver was used to determine a constant that, when multiplied by the relative incidence, resulted in the right- and left-hand sides of Equation 2 becoming equal. This resulted in the estimated annual number of new cases to change over time.

When immigration from endemic high-risk countries was highlighted as an important source of new infections, the annual number of new cases due to immigracalculated by gathering tion was net annual immigration, by country of origin and from national databases, regarding the anti-HCV prevalence in the country of origin. Studies in Germany showed that prevalence in the Turkish population living in Germany was similar to those living in Turkey [9,10]. In countries where immigration was highlighted, the estimated annual number of new infections had two components - acute infections and immigrants. The forecasted disease burden was similar when new cases, due to net immigration. were grouped with acute infections vs. when they were treated as a separate population. In countries that reported age-specific data, the average age of immigrants was found to be 30 years. The viremic rate ranged from 62-82% [4], and 65-85% of acute infections progressed to chronic infections [6-8]. By grouping the immigrant cases with the acute cases, the progression to chronic HCV had the same impact as if the same population were adjusted for per cent viremic.

In the second step, the age and gender of the acute infections were calculated using the age and gender distribution of the total infected population in a given year. The Excel<sup>®</sup> optimization add-in, Frontline Solver, was used to back-calculate the age and gender distribution of the new infections in 1966 and every five years thereafter until the year of known distribution in the total infected population. The age and gender distribution in years 1950-1965 was set to equal to 1966 and trended linearly between the 5year increments. Constraints were used to limit how the number of new infections was allocated by age and gender  $- \leq 5\%$  of new cases in a given year could be allocated to age cohort <14, and 70-85+ years old and  $\leq 20\%$  of new cases could be allocated to age cohorts between 15-69 years old. These constraints were relaxed when country-specific information was available regarding high level of infections in given years. For example, in countries where IDU was a major risk factor, the per cent of new infections allocated to specific age groups was increased.

## Progression rates

Disease progression was simulated by multiplying the total number of cases at a particular stage of the disease by a progression rate to the next stage (Fig. 1). The rates were gathered from previous studies [6–8,11–16] or calculated using known number of HCC cases/mortality as explained below.

Fibrosis progression rates were derived from US data (Table 1). The reported number of new annual liver cancers (by gender) and liver cancer deaths in 1999-2009 from the US Surveillance, Epidemiology and End Results (SEER) programme was used to back-calculate the fibrosis progression rates required in the model to match published data. It was assumed that 90% of all liver cancers were HCC [17], and 36-40% of HCC cases were due to HCV [18,19]. Age-specific progression rates in the UK were used as guidance when back-calculating progression rates [20]. In this model, the UK data provided the most satisfactory results when compared to similar studies in other countries [12.13.21]. When actual number of HCV-related HCC cases, HCC deaths or decompensated cirrhosis cases was available in a country, the fibrosis progression rates were modified to fit reported data. In France, previously published progression rates were used [22]. In Egypt and Turkey, the F1-F2 progression rate was reduced by 20% to account for lower alcohol consumption. In Australia, the Kirby Institute reported the annual number of HCV cases by disease state [23]. The F1-F2, F2-F3 and F3-F4 were increased by 25% to fit reported data. This increase could be attributed to high rates of alcohol intake and a predominantly male-infected population [13]. In Portugal, a flat progression rate for all ages provided a more satisfactory result. The progression rates used in Portugal were as follows: F0 to F1 (11.7%), F1 to F2 (8.5%), F2 to F3 (12%), F3 to F4 (11.6%). In Egypt, the spontaneous clearance rate for the new infections was set to 33% (15–45%) among males and 45% (15-45%) among females. Additionally, the spontaneous clearance rate for both genders was 26.2% (22.7-30.2%) in England and 23% (15-45%) in Canada.

The number of new cases at a stage of the disease (*New Cases*  $_{\text{stage x}}$ ) was calculated by multiplying the progression rate and the total number of cases at the previous stage of the disease in the previous year (*Total Cases*  $_{\text{stage x-1, Year}}$   $_{Y-1}$ ). As shown in Equation 1, the total number of cases was adjusted for aging, all-cause mortality and cured in any given year.

## All-cause mortality

The all-cause mortality rates by age and gender were gathered from the Human Mortality Database [24] unless stated otherwise. The rates were adjusted for incremental increase in mortality due to injection drug use (IDU) and transfusion, as described previously [25]. Unless specified, a standard mortality ratio (SMR) of 10 (9.5–29.9) was used for the portion of the HCV-infected population who were active IDU between ages 15 and 44 [26–31]. An SMR of 2.1 (1.3–17.6) was applied to all ages for the portion of the population infected due to transfusion [32]. In all countries studied, new HCV infections due to transfusion were no longer a risk factor. A linear declining rate was applied to get the per cent of total infections attributed to transfusion to zero by 2030. When country-specific all-cause mortality rate among HCV cases was available, it was used in place of the above mortality model.

#### Australia

Based on expert consensus, it was estimated that 38% of the infected population were active IDU in 2013. A national study reported that 1.2% of the viremic population were infected through transfusion [33].

#### Austria

In 2008, it was estimated that 24.6% of the HCV population were active IDU and 25% of the population were infected through transfusion [34].

#### Belgium

In 2004, IDU (27%) and blood transfusion (23%) were the primary risk factors for HCV [35].

# Brazil

Based on data from a national study, it was estimated that 5.1% of the prevalent population were active IDU and that 14.8% of the prevalent population were infected through transfusion [36].

#### Canada

It was estimated that 22% of the prevalent population were active IDU and 11% were infected through transfusion in 2007 [37].

#### Czech Republic

It was estimated that in 1998, transfusion accounted for 15% of the HCV infection [38]. Transmission of HCV infection through transfusion has been declining since 1998 and is no longer considered a risk factor. The most common route of HCV transmission is through IDU. In 2012, 65.2% of individuals diagnosed with HCV reported past or present IDU [39]. In 2007, it was estimated that 32.4% of IDUs entering weaning programmes were anti-HCV positive [40].

# Denmark

Only 4.6% of HCV infections were due to transfusion exposures in 2009 [41]. By contrast, 30% of HCV infections were active IDU. An IDU SMR of 18 was chosen, as it results in an annual IDU mortality of  $\sim$ 2%, which was

Table 1 HCV dise	ase pri	ogressi	on rates															
Age cohorts	0-4	5-9	10 - 14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60–64	65–69	70–74	75-79	80-84	85+
Back-calculated pr	cogress	ion ra	tes – mal	les, %														
F0 to F1	5.3	5.3	6.4	6.4	5.2	5.2	3.8	3.8	13.9	13.9	17.1	17.1	19.4	19.4	21.8	21.8	17.9	17.9
F1 to F2	3.8	3.8	4.7	4.7	3.8	3.8	2.7	2.7	10.1	10.1	12.4	12.4	14.1	14.1	15.8	15.8	13.0	13.0
F2 to F3	5.4	5.4	6.6	6.6	5.3	5.3	3.9	3.9	14.3	14.3	17.5	17.5	19.9	19.9	22.4	22.4	18.3	18.3
F3 to Cirrhosis	0.0	0.0	0.8	0.8	2.5	2.5	5.7	5.7	8.8	8.8	4.8	4.8	9.9	9.9	19.1	19.1	19.1	19.1
F3 to HCC	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.2	0.2	0.3	0.3	0.3	0.3
Cirrhosis to	0.3	0.3	0.3	0.3	0.3	0.3	0.5	0.5	0.9	0.9	1.4	1.4	2.4	2.4	3.9	3.9	3.9	3.9
HCC																		
Back-calculated pr	cogress	sion ra	tes – fema	ales, %														
F0 to F1	4.4	4.4	5.4	5.4	4.3	4.3	3.1	3.1	11.6	11.6	14.3	14.3	16.2	16.2	18.2	18.2	14.9	14.9
F1 to $F2$	3.2	3.2	3.9	3.9	3.1	3.1	2.3	2.3	8.4	8.4	10.4	10.4	11.7	11.7	13.2	13.2	10.8	10.8
F2 to $F3$	4.5	4.5	5.5	5.5	4.4	4.4	3.2	3.2	11.9	11.9	14.6	14.6	16.6	16.6	18.6	18.6	15.3	15.3
F3 to Cirrhosis	0.0	0.0	0.6	0.6	2.1	2.1	4.7	4.7	7.4	7.4	4.0	4.0	8.3	8.3	15.9	15.9	15.9	15.9
F3 to HCC	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2
Cirrhosis to	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.7	0.7	1.2	1.2	2.0	2.0	3.3	3.3	3.3	3.3
HCC																		
Disease progressio	u								Repo	orted pro	gression	rates					Source	
Acute HCV sponts	meous	clears	ince							18.0%	(15.0-45)	(%0.9						[6-8]
Diur sens ascites t	o diur	refrac	tory ascit	tes						6.7%	(4.0-9.4)	(%					[6-8,1]	[-16]
Diur sens ascites t	o liver	relate-	d death							11.0%	(7.7 - 14.	3%)					[6-8,1]	[-16]
Variceal hem. to l	iver-re	lated c	leath (ye	ar 1)						40.0%	(33.4-46	(%)					[6-8,1]	[-16]
Variceal hem. to l	iver-re	lated c	leath (sul	byears)						13.0%	(8.5 - 17.	5%)					[6-8,1]	[-16]
Hepatic enceph. to	) liver-	-relatec	ł death (y	year 1)						68.0%	(65.9–70	(.1%)					[6-8,1]	[-16]
Hepatic enceph. to	) liver-	-relatec	ł death (s	subyears)						40.0%	(37.8-42	2.2%					[6-8,1]	[-16]
Diur refractory as	cites to	o liver-	related de	eath						33.0%	(28.0–38	(%0.8)					[6-8,1]	[-16]
HCC to liver-relate	ed deai	th (yea	ur 1)							70.7%	(43-77.0	(%(					[15	,106]
HCC to liver-relate	ed deai	th (sul	years)							16.2%	(11-23.(	(%(						[106]
Liver transplant to	o liver-	-relateo	l death (y	year 1)					33.1	-10.7%	(SD 2.8–	0.4%)					[]	,107]
Liver transplant to	o liver-	-relatec	l death (s	subyears)					G	.9-4.8%	(SD 7.6–	1.0%)					[3	,107]

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consistent with the literature [42,43]. Nosocomial transmission was associated with 5% of cases reported to the National Registry of Communicable Diseases in 2009– 2011. Fewer than half of these infections were acquired in Denmark before screening of blood donors was initiated in 1991, with the remainder originating from hospitals outside of Denmark [44–46]. Sexually transmitted cases were on the rise, with an incidence of HCV infection of 0.4% in the MSM population [47].

# Egypt

Background mortality rates by age group and gender from 1950 to 1989 were calculated using United Nations (UN) mortality data [48]. For 1990–2011, mortality rates reported by the World Health Organization (WHO) were used [49].

It was estimated that 0.5% of the prevalent population were active IDU based upon the HCV prevalence rate in Egyptian IDU [50] and total IDU population in Egypt [51]. It was estimated that 24.3% of the prevalent population were infected through transfusion, according to EDHS [52]. Excess diabetes in the HCV prevalent population, as compared to the general population, was 9.7% [53], and a standard hazard ratio for hospitalization was used as an analogue for excess mortality in this population (SMR = 2.1) [54].

### England

In 2004, there were an estimated 59 100 active IDU with HCV (40%) [55]. From 1996 to 2012, 2% of laboratories reported transfusion as a risk factor [55].

# France

Based on data from a national study, it was estimated that 26% of the prevalent population were IDU and that 35% were infected through transfusion in 2004 [56].

#### Germany

An estimated 45.5% of the infected population reported a primary risk factor for IDU [57], and approximately one-third was thought to be active IDU. Approximately 17.4% of HCV infections were from transfusion [57].

# Portugal

Age group and gender-specific mortality rates from the National Institute of Statistics (INE) were used for years 1982–2012 [58]. Using published data and expert panel input, it was estimated that 1% of the overall infected population was active IDU in 1980, increasing to 12.8% in 2000, then decreasing to 7.9% in 2005, and finally decreasing to 1% in 2012 and continuing at 1% thereafter [59,60]. Increased mortality among active IDU was estimated using an SMR of 11.6 for individuals between 15 and 44 years of age. This was based on a study of drug-related mortality in eight European countries, including

Portugal [61], and was adjusted to account for gender differences [58,62]. It was estimated that 15.2% of the HCV population were infected through transfusion [63].

### Spain

All-cause mortality rates for the years 1970–2011 were estimated by 5-year age and gender cohorts using death statistics from INE [64]. It is estimated that from 1994 to 1996, transfusion accounted for 25.5% of the transmission of HCV infection, whereas past or present IDU accounted for an estimated 10% [65]. Transmission of HCV infection through transfusion and IDU has been declining since 1996. Currently, the most common route of HCV infection is through nosocomial infection, accounting for approximately 73% of infections in 2005 [66].

# Sweden

The non-liver-related mortality in the HCV cohort in Sweden was studied in detail and published [67]. A separate adjustment for IDU and transfusion risk factors was not necessary. Increased mortality among the HCV viremic population was accounted for using SMRs by 5-year age and gender cohorts, as identified through the Swedish HCV cohort from 1990 to 2003. SMRs were calculated using a 6-month lag time after HCV notification to reduce the risk of selection bias.

# Switzerland

Mortality data by the Swiss Federal Statistics Office (FSO) [68] were used to estimate rates for all-cause mortality. An SMR of 5.5 was used for active IDU cases due to the effective harm reduction systems in place for people who use drugs. Approximately 21% (15 000) of the anti-HCV positive population were active IDU. This figure was derived from an estimated total of 25 000 people [69] with problematic heroin use and an anti-HCV prevalence of approximately 60% [70,71]. Approximately 11% of HCV infections were from transfusion [72].

#### Turkey

All-cause mortality for the years 2009–2012 was estimated using published death statistics from the Turkish Statistical Institute [73–75]. Historical mortality for the years 1950–2008 was estimated using 5-year Turkish death statistics provided by the UN [76]. It is estimated that transfusions accounted for 35.3% of the transmission of HCV infection, whereas past or present IDU accounted for an estimated 1.4% [77].

# Diagnosed

The total number of diagnosed cases was collected and reported previously [4]. To estimate current and future total diagnosed cases, it was assumed that the number of newly diagnosed cases stayed the same as the last reported year.

# Treated & cured

As described previously [4], analysis of pegylated interferon (Peg-IFN) or ribavirin (RBV) units sold, or national data, were used to estimate the total number of treated HCV patients. It was assumed that the number of treated patients stayed constant between 2011 and 2013. It was also assumed that the number of treated patients for each genotype was proportional to the genotype distribution of the HCV-infected population [4].

The annual number of cured patients was estimated using the average sustained viral response (SVR) rate in a given year. A separate average SVR was used for the major genotypes, as shown in Table 2. Different methods were used to estimate the average SVR. All countries took into consideration a weighted average of different treatment options in a given year - interferon-based therapy in combination with RBV (dual therapy) or with RBV and a protease inhibitor (PI) (triple therapy). Some also took into consideration the percentage of the population who were treatment experienced and treatment naïve on each treatment option, while other countries took into account the disease stages of the patients being treated (e.g. F1, F2, F3) and F4). In 2013, the average SVRs for all countries studies were as follows: G1 - 53% (38-70%). G2 - 72% (50-90%), G3 - 64% (40-71%), G4 - 50% (38-61%). The country-specific SVR by genotype is shown in Table 2.

The number of cured patients from all genotypes was summed by stage of the disease and distributed proportionally among age eligible cohorts (see below). If the treatment protocols in a country recommended treatment of patients aged 20–69, the number of cured patients was distributed based on the number of cases in each cohort between ages 20 and 69, and it was assumed that no one younger than 20 or older than 69 was treated and cured.

# Treatment protocols

The pool of patients who could be treated was impacted by explicit or implicit treatment protocols. Explicit protocols were determined by national or international guidelines, whereas implicit protocols were determined by actual practice in the country. In 2013, decompensated cirrhotic patients were considered ineligible in all countries.

According to the literature, approximately 40–60% of HCV patients are eligible for Peg-IFN/RBV [78,79]. The definition of eligibility included contraindications to the drugs (e.g. psychiatric conditions) as well as patient's preference. In this analysis, 20-65% of the patients were considered treatment eligible (Table 2) for standard of care. The standard of care varied across countries and genotypes. High and low SVR rates for genotype 1 (Table 2) were indicative of availability of triple therapy (Peg-IFN + RBV + PI). High SVR rates were observed when triple therapy was made available to early-stage genotype 1

patients, while low SVR rates were observed when triple therapy was restricted to patients with late-stage liver disease. The numbers reported here represent a weighted average of all patients and therapies.

In each country, the expert panel provided the most common stages of fibrosis considered for treatment (see Table 2). Many countries use, or are starting to use, non-invasive testing methods to determine the level of fibrosis on patients. However, the Metavir scale is still the gold standard, and it was used in this model to represent the severity/stage of liver fibrosis. The age of the patients was also considered. Table 2 outlines the most common age bands considered for treatment. The data presented here do not imply that patients with lower Metavir score or older/younger patients were not treated in each country. Instead, the data provided a range for the majority of treated patients.

## Future treatment protocols

In this analysis, it was assumed that the future treatment paradigm will remain the same as today. Thus, all assumptions (the number of acute cases, treated patients, per cent of patients eligible for treatment, treatment restrictions, the number of newly diagnosed annually and the average SVR by genotype) were kept the constant in future years.

# RESULTS

The results of the analysis for 2013 are shown in Table 2. Figure 2 shows the age distribution of the HCV-infected population by country. Table 3 compares the change in HCV disease burden in 2013 and 2030, while Figs 3 and 4 show the projected HCV disease burden between 1950 and 2030. It should be noted that decompensated cirrhosis figures excluded those who received a liver transplant.

## Australia

Changes over time in incidence were based upon published estimates of annual new cases [80]. New cases peaked in 1999 and have since declined, with the main risk factor being IDU [33]. An estimated 8900 new cases occurred in 2013.

Based on expert consensus, it was estimated that approximately 50% of treated patients in 2013 were classified as F0/1 with the remaining patients classified as F2/3 or cirrhosis.

In 2013, the total number of viremic infections was estimated at 233 400 (179 000–246 000) and is projected to peak in 2025 at 254 600 cases and increase by 5% from 2013 to 2030. The number of HCC cases in 2013 was estimated at 590 cases and is forecasted to increase by 245% by 2030. Similarly, the number of liver-related deaths will increase by 230% from a base of 530 deaths, while decompensated and compensated cirrhosis will

	Australia	Austria	Belgium	Brazil	Canada	Czech Republic	Denmark	Egypt
Country's population (000)	23 200	8400	10 800	200 100	35 000	10 600	5600	82 600
Total viremic infections (000)	233 (180–250)	25 (8–35)	67 (25–80)	1940 (1410–2200)	252 (180–315)	43 (22–52)	21 (17–27)	5989 (4575–6705)
Viremic prevalence (%)	1.0 (0.8–1.1)	0.3 (0.1-0.4)	0.6 (0.2-0.7)	1.0 (0.7–1.1)	0.7 (0.5-0.9)	0.4 (0.2-0.5)	0.4 (0.3-0.5)	7.3 (5.5–8.1)
Total diagnosed (viremic)								
Total cases	200 500	9400	28 700	300 000	176 400	13 100	12 300	868 700
Annual newly diagnosed	8400	600	2900	10 000	7600	800	700	110 000
Diagnosis rate (%)	86	37	43	15	70	31	59	15
Newly diagnosed rate (%)	3.6	2.4	4.2	0.5	3.0	1.9	3.3	1.8
Treated & cured								
Annual number treated	2600	1100	710	11 700	3600	880	100	65 000
Annual number cured	1500	700	380	5000	3000	480	09	31 200
Average SVR (%)	58	64	54	43	83	55	60	48
Treatment rate (%)	1.1	4.2	1.1	0.6	1.4	2.1	0.5	1.1
New infections								
Total cases	8800	580	910	12 700	5600	1 400	350	168 400
Infection rate (per 100K)	38	7	8	6	16	13	6	204
New CHC cases	7200	470	690	10 400	4300	1200	290	102 300
Risk factors								
Number of active IDU	88 700	6250	18 120	98 880	54 560	13 790	6290	9980
% Active IDU	38	25	27	5	22	32	30	0.2
Previous blood transfusion	1980	4910	10 090	286 930	26 910	750	780	1 455 360
% Previous blood transfusion	1	19	15	15	11	2	4	24
Mortality								
All cases	2230	420	1160	34 700	2820	400	330	153 500
All cause mortality	1700	320	870	25 700	2100	320	250	120 500
Liver related mortality	530	100	290	0006	720	80	80	33 000
Current treatment protocols								
Treatment age	20 - 69	15 - 69	15 - 84	15 - 69	15 - 64	15 - 85+	15 - 64	15 - 59
% Treatment eligible	09	50	09	09	60	09	09	50
Treated stages - G1	>= F0	>= FI	>= F2	>= F2	>= F2	>= F0	>= F2	>= F2
Treated stages - G2	>= F0	>= Fl	>= F0	≻= Fl	>= F2	>= F0	>= F2	>= F2
Treated stages - G3	>= F0	>= FI	>= F2	>= FI	>= F2	>= F0	>= F2	>= F2
Treated stages - G4	>= F0	>= F1	>= F2	>= Fl	>= F2	>= F0	>= F2	>= F2
SVR - G1 (%)	47	60	60	38	60	48	44	48
SVR - G2 (%)	75	90	65	50	70	70	74	70
SVR - G3 (%)	70	70	40	50	70	70	71	70
SVR - G4 (%)	60	50	40	38	48	48	60	48

Table 2 HCV-infected population and treatment forecasts in 2013

	Encland	France	Germany	Portneal	Snain	Sweden	Switzerland	Turkey
Country's population (000)	53 700	63 800	81 800	10 700	47 000	9500	7900	76 500
Total viremic infections (000)	144 (105–210)	195 (80-245)	267 (150–385)	125 (95–140)	473 (370–550)	41 (18–45)	83 (37–95)	514 (315-600)
Viremic prevalence (%)	0.3 (0.2-0.4)	0.3 (0.1-0.4)	0.3 (0.2-0.5)	1.2 (0.9–1.4)	1.0 (0.8–1.2)	0.4 (0.2-0.5)	1.0 (0.4–1.1)	0.7 (0.4-0.8)
Total diagnosed (viremic)								
Total cases	49 700	134 100	153 000	40 800	190 100	32 800	32 600	81 300
Annual newly diagnosed	5600	0006	4000	1300	15 300	1500	1100	5500
Diagnosis rate (%)	35	69	57	33	40	81	39	16
Newly diagnosed rate (%)	3.9	4.6	1.5	1.0	3.2	3.8	1.3	1.1
Treated & cured								
Annual number treated	5400	10 100	12 700	800	9800	1100	1100	4200
Annual number cured	3800	5300	7000	700	4900	600	700	2000
Average SVR (%)	70	52	55	88	50	55	64	48
Treatment rate (%)	3.8	5.2	4.7	0.7	2.1	2.8	1.3	0.8
New infections								
Total cases	4000	4200	5000	810	2800	1400	1050	5300
Infection rate (per 100K)	7	7	6	8	6	15	13	7
New CHC cases	2900	3400	4100	670	2300	1100	860	4400
Risk factors								
Number of active IDU	56 900	50 600	40 400	1250	16560	12 200	17 400	2420
% Active IDU	40	26	15	1	4	30	21	0.5
Previous blood transfusion	2400	44 600	29 200	11 580	12 060	1800	8100	134 190
% Previous blood transfusion	2	23	11	6	3	4	10	26
Mortality								
All cases	1490	4900	5200	1560	5500	930	980	10 300
All cause mortality	1100	3300	3900	670	3600	760	009	8300
Liver related mortality	390	1600	1300	890	1900	170	380	2000
Current treatment protocols								
Treatment age	15 - 64	15 - 74	0 - 74	15 - 64	15 - 64	20 - 69	15 - 69	15 - 79
% Treatment eligible	09	09	50	65	50	09	09	20
Treated stages - G1	>= F0	>= F0	>= F0	>= F2	>= F2	>= F2	>= F2	>= F0
Treated stages - G2	>= F0	>= F0	>= F0	>= F2	>= Fl	>= F0	>= F2	>= F0
Treated stages - G3	>= F0	>= F0	>= F0	>= F2	>= Fl	>= F0	>= F2	>= F0
Treated stages - G4	>= F0	>= F0	>= F0	>= F2	>= F2	>= F2	>= F2	>= F0
SVR – G1 (%)	70	48	48	48	48	40	61	48
SVR - G2 (%)	70	70	70	80	85	73	70	70
SVR - G3 (%)	70	60	70	70	50	65	70	48
SVR - G4 (%)	48	55	48	09	48	40	61	48

Table 2 (continued)

increase by 190% and 175% from a base of 1430 and 13850 cases in 2013.

# Austria

The annual number of new cases is considered to have peaked in 1991 due to high-risk behaviours and a contaminated blood supply, and then to have decreased sharply following blood screening and harm reduction efforts. In 2013, it was estimated that there were 580 new infections.

The total number of viremic infections peaked in 2003, with 30 100 cases, declined to 25 400 (8320–34 500) by 2013 and is forecasted to further decline to 14 000 cases by 2030. The number of HCC cases in 2013 was estimated at 110 cases and was forecasted to increase by 35% by 2030. Similarly, the number of liver-related deaths will increase 25% from a base of 100. Decompensated cirrhosis and compensated cirrhosis infections will peak in 2020, at 25% and 10% above the 2013 base of 200 and 2450, and will then decrease to 10% and 20% of the base.

## Belgium

The annual number of new cases is considered to have peaked in 1989 due to high-risk behaviours and a contaminated blood supply, and then to have decreased sharply following blood screening and harm reduction efforts. In 2013, it was estimated that there were 910 new infections.

The total number of viremic infections peaked in 2003, with 72 900 cases, declined to 67 100 (24 800–78 600) by 2013 and is forecasted to further decline to 47 700 by 2030. The number of HCC cases in 2013 was estimated at 300 cases and was forecasted to increase by 110% by 2030. Similarly, the number of liver-related deaths will increase by 95% from a base of 290, while decompensated cirrhosis and compensated cirrhosis infections will increase 70% and 65% from a base of 820 and 7060 in 2013.

# Brazil

It was estimated that new cases peaked in 1999 and have since declined, due to the widespread adoption of blood screening, to an estimated 11 200 new cases in 2013.

The total number of viremic infections peaked in 1996, with 2 255 000 cases, declined to 1 938 700 (1 411 500–2 098 700) cases by 2013 and is forecasted to further decline by 35% by 2030. The number of HCC cases in 2013 was estimated at 9710 cases and was forecasted to increase by 95% by 2030. Similarly, the number of liver-related deaths will increase by 85% from 9000 deaths in 2013. Cases of decompensated and compensated cirrhosis will increase 65% and 45% from a base of 27 500 and 222 090 cases in 2013, respectively.

### Canada

Relative changes in incidence by year were derived from a Public Health Agency of Canada analysis that included historical estimates of new cases [81]. The peak of new cases occurred in 1982, with IDU being the main risk factor [37]. In 2013, 5570 new cases are estimated to have occurred.

The total number of viremic infections peaked in 2003, with 260 000 cases, declined to 252 000 (177 900–314 800) cases by 2013 and is forecasted to further decline by 15% by 2030. The number of HCC cases in 2013 was estimated at 730 cases and was forecasted to increase by 190% by 2030. Similarly, the number of liver-related deaths will increase by 150% from 720 deaths in 2013. Cases of decompensated and compensated cirrhosis will increase 90% and 95% from a base of 1790 and 18 510 cases in 2013, respectively.

# Czech Republic

The annual number of new cases is considered to have peaked in 1999 and began to steadily decrease thereafter. It is believed that the number of new cases arising annually is relatively stable in the light of continued transmission through IDU. In 2013, there were an estimated 1400 new cases of HCV.

In 2013, the total number of viremic infections was estimated at 42 500 (21 600–51 800), and it was forecasted to increase to 43 300 cases in 2022 before declining to 42 200 by 2030. The number of HCC cases in 2013 was estimated at 90 cases, and it was forecasted to increase by 85% percentage by 2030. Similarly, the number of liverrelated deaths will increase by 90% from a base of 80, while decompensated and compensated cirrhosis will increase 100% and 105% from a base of 190 and 1830 in 2013.

# Denmark

The annual number of new cases is considered to have peaked around 1990 due to high-risk behaviours and gradually decreased as interventions aimed at drug treatment centres and prisons became available in the late 1990s. Voluntary blood donation without financial compensation as well as strict exclusion and quarantine criteria for donors are believed to have limited the spread of the virus from reaching the wider population [82, 83]. Additionally, needle exchange programmes, opium substitution therapy and immunization against hepatitis B have had an impact on keeping co-infection with hepatitis B and HIV low [41].

Back-calculating from estimates of "new" IDU incidence of approximately 575 persons a year (2009) [84] and assuming that 50% of IDU were chronically infected with HCV provided an estimated rate of 288 new viremic cases per year. This was adjusted by an additional 5% to



Fig. 2 Distribution of the 2013 HCV-infected population by age as a percentage of total number of cases.

account for imported cases (migrants), resulting in 303 new viremic cases annually. In 2013, it was estimated that there were 350 new infections.

The total number of viremic infections peaked in 2006, with 21 400 cases, declined to 20 900 (16 700–22 500) by 2013 and is forecasted to further decline to 17 200 by 2030. The number of HCC cases in 2013 was estimated at 90 cases and was forecasted to increase by 140% by 2030. Similarly, the number of liver-related deaths will increase by 130% from a base of 80, while decompensated cirrhosis and compensated cirrhosis infections will increase 110% and 95% from a base of 230 and 1870 in 2013.

# Egypt

The annual number of new cases was based upon expert consensus and validated using predicted ranges for incidence from other analyses [85]. The estimated peak number of new cases occurred in 1970, with a high rate of annual new cases thereafter, given ongoing transmission through nosocomial and other routes [86]. There were an estimated 168 600 new cases in 2013.

The total number of viremic infections peaked in 2002, with 6 539 000 cases, declined to 5 979 800 (4 566 900–6 694 600) cases by 2013 and is forecasted to further decline by 26% by 2030. The number of HCC cases in 2013 was estimated at 16 050 cases and is forecasted to increase by 15% by 2030. Similarly, the number of liver-related deaths will increase by 10% from 32 950 deaths in 2013. Decompensated cirrhosis infections will peak in

2016, at 7% above the 2013 base of 137 200, and will increase 0.6% from 2013 to 2030. Compensated cirrhosis infections will peak in 2021 at 7% above the 2013 base of 626 160 and will decrease 2% during 2013–2030.

# England

The annual number of new cases is considered to have peaked in 1990 due to a contaminated blood supply and then decreased as a result of blood screening. A second peak around 2000 was modelled due to continued IDU behaviours, based on self-reported needle sharing from 1991 to 2011 [87]. IDU is still the most common route of transmission, accounting for 90% of laboratory reported cases between 1996 and 2012 [55]. In 2013, it was estimated that there were 3980 new infections.

The total number of viremic infections peaked in 2007, with 153 000 cases, declined to 144 000 (103 000–174 000) by 2013 and is forecasted to further decline to 83 700 by 2030. The number of HCC cases in 2013 was estimated at 410 cases and was forecasted to increase by 125% by 2030. Similarly, the number of liver-related deaths will increase by 100% from a base of 390, while decompensated cirrhosis and compensated cirrhosis infections will increase 60% and 55% from a base of 860 and 9500 in 2013.

### France

Annual incidence was derived from data from a US study [81] that was adjusted to match outputs from a French

	Turkey		514 000	352 000	(30)		2230	3770	70		2020	3420	70		5590	8820	60		51 100	71 200	40
	Switzerland		82 700	63 200	(25)		400	740	85		380	650	70		1140	1790	55		8520	12 700	50
	Sweden		40 600	31 900	(20)		270	290	10		170	170	-		430	360	(15)		3890	3430	(10)
	Spain		473 000	285 000	(40)		2210	4500	105		1940	3750	95		4230	6710	60		46 200	72 700	55
	Portugal		125 000	87 400	(30)		1150	2050	80		890	1700	90		2410	4910	105		17 900	25 600	45
	Germany		267 000	121 000	(55)		1530	1640	10		1300	1430	10		2430	2200	(10)		31 100	24 400	(20)
	France		195 000	85 100	(55)		1770	300	(85)		1570	380	(75)		3650	760	(80)		29 100	5770	(80)
	England		144 000	83 700	(40)		410	920	125		390	770	100		860	1370	09		9500	14 700	55
	Egypt		5 980 000	4 420 000	(25)		16 100	18 300	15		33 000	36 500	10		137 000	136 000	(1)		626 000	611 000	(2)
	Denmark		20 900	17 200	(20)		90	210	140		80	180	130		230	480	110		1870	3670	95
	Czech Republic		42 500	42 200	0		90	170	85		80	160	90		190	390	100		1830	3740	105
md 2030	Canada		252 000	209 000	(15)		730	2090	190		720	1800	150		1790	3370	90		18 500	36 100	95
in 2013 a	Brazil		1 940 000	1 250 000	(35)		9710	18 900	95		0006	16 620	85		27 500	45 000	65		222 000	323 000	45
e burden	Belgium		67 100	47 700	(30)		300	640	110		290	570	95		820	1400	70		7060	11 500	65
JV diseas	Austria		25 400	13 900	(45)		110	150	35		100	130	25		200	180	(10)		2450	2010	(20)
ison of H(	Australia	tions	233 000	251 000	5		590	2030	245	lity	530	1740	230	rhosis	1430	4150	190	osis	13 800	37 900	175
Table 3 Compar		Viremic HCV infec	2013 Est.	2030 Est.	% Change	HCC cases	2013 Est.	2030 Est.	% Change	Liver related morta	2013 Est.	2030 Est.	% Change	Decompensated cirr	2013 Est.	2030 Est.	% Change	Compensated cirrho	2013 Est.	2030 Est.	% Change

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Fig. 3 Change in HCV disease burden over time.

HCV model [12]. The estimated peak number of new cases occurred in 1989, with IDU and blood transfusion identified as risk factors associated with infection [56]. There were an estimated 4200 new cases in 2013.

The total number of viremic infections peaked in 2000, with 274 740 cases, declined to 195 220 (80 650–201 100) cases by 2013 and is forecasted to further decline by 56% by 2030. The number of HCC cases will

peak at 1790 cases in 2014 and was forecasted to decrease by 83% from 2013 to 2030. Similarly, the number of liver-related deaths will peak in 2015 at 1630 deaths and will decrease by 76% from 2013 to 2030. Cases of decompensated cirrhosis will peak at 3670 cases in 2014 and will decrease 79% from 2013 to 2030. Cases of compensated cirrhosis peaked at 29 100 cases in 2013 and will decrease 80% from 2013 to 2030.



Fig. 3 (Continued).

# Germany

Today, IDU serves as the primary risk factor for HCV; however, this has not always been the case. In 1978–1979, 2867 young women received HCV genotype 1b-contaminated anti-D immunoglobulin during pregnancy [88]. The single-source outbreak was contained within this cohort, which has since been well documented and followed up [88–90]. Prior to 1990, when blood screening was introduced, individuals were predominantly infected with HCV via blood transfusions with contaminated blood. Once blood screening was initiated, the number of acute infections began to decrease; however, high-risk IDU behaviours allowed for continued infection. In 2013, it was estimated that there were 4980 new infections.

Individuals entering the country with an HCV infection have also influenced the historical distribution of new cases. Waves of immigration from the former Soviet Union,



Fig. 4 Change in the number of liver transplants, decompensated cirrhosis cases and HCC cases over time.

Turkey and other Mediterranean countries are thought to have contributed to the estimated 27–37% of infected individuals reporting a nationality other than German [57,91,92]. Predominant nationalities include Russian (19–24%), Eastern European (11–15%) and Turkish (4–6%) [57,91,92]. A study conducted among Turks living in



Fig. 4 (Continued).

Turkey and Turks living in Germany found that the anti-HCV prevalence is similar among both groups, indicating that the HCV prevalence among immigrants may be best

estimated by the prevalence of their home country [9,10]. In 2012, there were more than seven million foreign residents and naturalizations [93,94]. Of these, an estimated

55% were of Turkish origin and 12.5% originated from a post-Soviet state. Region-specific estimates of HCV prevalence from Hope 2013 and Mohd Hanafiah 2013 were used to estimate the viremic HCV prevalence among immigrants and naturalized citizens [1,34]. In total, 140 000–167 000 foreign cases of viremic HCV were estimated in 2012. This corresponds to  $\sim$ 34% of the total cases of viremic HCV.

The total number of viremic infections peaked in 2003, with 315 000 cases, declined to 267 000 (152 000–383 000) by 2013 and is forecasted to further decline to 121 000 by 2030. The number of HCC cases in 2013 was estimated at 1530 cases and was forecasted to increase by 10% by 2030. Similarly, the number of liver-related deaths will increase by 10% from a base of 1300. Decompensated cirrhosis and compensated cirrhosis infections will peak in 2021 and 2019, at 10% above the 2013 base of 2430 and 31 090, and will then decrease to 10% and 20% of base.

# Portugal

To estimate variations in annual incidence over time, historical facts related to the main means of HCV transmission were considered and correlated with available data on HIV diagnosis among IDU [95]. The estimated peak number of new cases occurred in 1992. There were an estimated 810 new cases in 2013.

The total number of viremic infections peaked in 2002, with 137 000 cases, declined to 125 400 (97 000–132 000) cases by 2013 and is forecasted to further decline by 30% by 2030. The number of HCC cases in 2013 was estimated at 1150 and was forecasted to increase by 80% by 2030. Similarly, the number of liver-related deaths will increase by 90% from 890 deaths in 2013. Cases of decompensated and compensated cirrhosis will increase by 105% and 45% from a base of 2410 and 17 920 cases in 2013, respectively.

### Spain

The annual number of new cases is considered to have peaked in 1991 before the implementation of blood screening protocols and began to decrease thereafter. It is believed that the number of new cases arising annually is relatively stable, in the light of continued transmission through nosocomial transmission. In 2013, there were an estimated 2810 new cases of HCV.

In 2013, the total number of viremic infections was estimated at 473 000 (371 000–546 000), and it was forecasted to have peaked at 530 000 cases in 2003 before declining to 285 000 by 2030. The number of HCC cases in 2013 was estimated at 2210 cases, and it was forecasted to increase by 105% by 2030. The number of liverrelated deaths will increase by 95% from a base of 1940, while decompensated cirrhosis and compensated cirrhosis will increase 60% and 55% from a base of 4230 and 46 200 in 2013.

# Sweden

The spread of HCV infection started comparatively late, near the end of the 1960s, with culmination in the 1970s as a result of increased IDU [96,97]. In the early 1990s, the number of new infections decreased gradually, but reached a plateau around the early 2000s. In 2013, it was estimated that there were 1400 new viremic infections.

The total number of viremic infections peaked in 2003, with 43 900 cases, declined to 40 600 (18 000–46 000) by 2013 and is forecasted to further decline to 31 900 by 2030. The number of HCC cases in 2013 was estimated at 270 cases and was forecasted to increase by 10% by 2030. Similarly, the number of liver-related deaths will increase by 1% from a base of 170. Decompensated cirrhosis and compensated cirrhosis infections will peak in 2016 and 2020, at 20% and 5% above the 2013 base of 430 and 3890, and will then decrease to 15% and 10% of base.

## Switzerland

Hepatitis C virus transmission peaked in the 1990s as a result of contaminated blood products, but decreased sharply once blood screening came into effect. Today, transmission of HCV occurs primarily through IDU [98]. In addition, the number of HCV cases is significantly influenced through immigration of individuals from HCV endemic countries [99–101].

In 2013, there were approximately 1050 (700–1100) new cases of HCV, of which an estimated 700 cases resulted from immigration [101]. From 2002 to 2011, 711 cases of acute HCV were declared in the country [102]. Assuming these declarations occurred primarily among symptomatic cases, and that only one in four cases of HCV are symptomatic [100], we estimated the true number of new infections to be around 3560 over the 10-year span. In the same period, it was estimated that as many as 7000 chronic HCV carriers migrated to the country [1,101,104]. Annually, this translates to 355 acute cases and 700 cases entering the country.

The total number of viremic infections peaked in 1996, with 88 600 cases, declined to 82 700 (37 300–93 000) by 2013 and is forecasted to further decline to 63 200 by 2030. The number of HCC cases in 2013 was estimated at 400 cases and was forecasted to increase by 85% by 2030. Similarly, the number of liver-related deaths will increase by 70% from a base of 380, while decompensated cirrhosis and compensated cirrhosis infections will increase 55% and 50% from a base of 1140 and 8520 in 2013.

# Turkey

The annual number of new cases was considered to have peaked in 1991 and began to steadily decrease thereafter. The number of new cases was relatively stable in the light of low rates of IDU. In 2013, there were an estimated 4910 new cases of HCV. This estimate included an increase due to immigration from former Soviet Republics with higher HCV prevalence.

In 2013, the total number of viremic infections was estimated at 514 000 (317 000–540 000), and it was forecasted to have peaked at 611 000 cases in 1998 before declining to 352 000 by 2030. The number of HCC cases in 2013 was estimated at 2230 cases, and it was forecasted to increase by 70% percentage by 2030. Similarly, the number of liver-related deaths will increase by 70% from a base of 2020, while decompensated and compensated cirrhosis will increase 60% and 40% from a base of 5590 and 51 100 in 2013.

# DISCUSSION

The previous publication [4] reported the historical number of total infections, viremic infections, diagnosed and treated cases. However, as the size of these populations changed over time, it was difficult to compare data from different countries and estimate treatment and diagnosis rates. In this study, the size of all populations was forecasted for 2013 using a mathematical model described above.

The total number of HCV infections reported here will be lower than those reported elsewhere, as this study focused on estimating the number of viremic cases in the population after taking into account all age groups, mortality, new infections and cured patients. For example, the HCV prevalence in Egypt was reported to be 14.7% in 15-59 year olds in 2008 [52], and the prevalence after adjusting for younger and older individuals was estimated at 12% [4]. However, only two-thirds of the infected population was viremic, resulting in a viremic prevalence of 8.5% in 2008. After taking into consideration mortality, new infections and cured patients, the 2013 viremic prevalence was estimated at 7.3% (Table 2). Although the viremic prevalence declined by 1.2%, the actual number of cases decreased by only 300 000 cases. The increase in Egypt's population in the last five years was responsible for some of the decline in estimated HCV prevalence [104].

The model took care to consider all key parameters that drive disease burden, to allow consistent estimates. It is important to note that the objective of this model was to develop forecasts consistent with best available data. However, the goal was not to develop accurate forecasts. The latter would require consideration of variables that were beyond the scope of this work, including policy and macroeconomic factors. Simplifying assumptions, as outlined in the methodology section, occurred and all attempts were

Table 4 The number of new	annual HCV cases required to
keep total infections in 2013	and 2030 constant

	Current number of new cases	Number of new cases required	% increase
Australia	8800	7810	-11
Austria	580	1310	126
Belgium	910	2330	156
Brazil	12 700	55 310	336
Canada	5600	9430	68
Czech Republic	1400	1260	-10
Denmark	350	630	80
Egypt	168 600	378 058	125
England	4000	7515	88
France	4200	13 097	212
Germany	5000	15 320	206
Portugal	810	9029	1015
Spain	2800	16 590	493
Sweden	1400	1910	36
Switzerland	1050	2360	125
Turkey	5300	17 400	228

made to provide full transparency. Table 2 and Fig. 2 provide sufficient data to support the conclusions stated here. For example, Fig. 2 shows that a large portion of the infected population in Egypt is older than in many other countries due to the time of peak infection. Table 2 shows that an estimated 168 400 new infections occurred in 2013, of which 102 300 went on to have chronic hepatitis C (CHC). In the same year, 31 200 cases were cured and 153 500 individuals with HCV died, resulting in a decline of 82 400 in the number of infections in 2013 alone.

As shown in Table 2, viremic HCV prevalence ranged from 0.3% in England to 7.3% in Egypt, with the highest diagnosis rate represented by countries with a centralized registry (Australia, Austria, Canada, Denmark, France. Germany, Sweden and Switzerland). Egypt, Brazil and Turkey were estimated to have the lowest diagnosis rate (15-16%), while Australia and Sweden estimated that more than 80% of their infected population has already been diagnosed. In addition, it was estimated that 0.5-4.6% of the infected population is newly diagnosed each year, with the lower end of the range represented by Brazil and the upper end of the range represented by France. France also has the highest treatment rate, with 5.2% of the infected population treated annually. This was followed by Germany at 4.7%, Austria at 4.2% and England at 3.8%. Of the countries studied, Denmark, Brazil, Portugal and Turkey had the lowest treatment rate (0.5%-0.8%).

The mortality (all-cause and liver-related) was driven by the age of the infected population (Fig. 2) and risk factors (Table 2). The older populations had a higher all-cause mortality rate. In addition, the disease progression rate increased with age (Table 1), and older individuals were more likely to have more advanced liver disease and associated liver-related deaths. As stated in the methodology section, active IDU cases also had a higher mortality rate due to the high-risk behaviour associated with injection drug use. Table 2 presents the percentage of the infected population who are actively injecting drugs. The all-cause mortality was adjusted accordingly for this portion of the population.

In each country, the details of the current treatment protocols were gathered. For the purpose of the model, it was assumed that the number of treated patients, eligibility, the number of newly diagnosed cases, SVR and treated patient segments would remain constant between now and 2030. This was not meant to be a realistic scenario, but was rather a baseline that could be used to compare the impact of new strategies to manage the future disease burden [105]. Thus, this work does not imply that the current treatment paradigm will remain as it is today. Instead, the scenarios shown here represent what would be the outcome if the current paradigm stayed the same.

This analysis forecasted that the total number of HCV infections is expected to decline in 2013–2030, except for the Czech Republic, which will remain flat (Fig. 3 and Table 3). As shown in Fig. 2, the infected population in Czech Republic is younger than other countries due to the later entrance of the epidemic, owing to geographical barriers, limited immigration from endemic countries and a delayed surge in IDU [4]. The age distribution of the HCVinfected population was determined from reported age and distribution, described in more detail elsewhere [4]. The model was calibrated to fit the historical data, and the outputs shown here were the result of aging of the infected population after taking into account new infections, mortality and cured. Countries where IDU was a key risk factor (e.g. Australia, Canada, Czech Republic, Denmark, England and Sweden) had a younger age distribution relative to the other countries studied, as most new infections occurred in young individuals in their early twenties and thirties. The same was true of countries where most of the HCV infections occurred recently (e.g. Czech Republic and Portugal). On the other hand, in countries where nosocomial infection was a major risk factor (Egypt and Turkey), an older infected population was observed. The majority of these infections occurred prior to 1990, and the new infections were not limited to youth.

The future number of HCV infections was determined by mortality, the number of cured patients and new cases. The relationship between mortality and the age distribution of the infected population was already discussed. The most dramatic example of the impact of treatment rate on the total number of HCV infections was observed in France, where a high level of treatment with Peg-INF/RBV starting in 2000 led to a marked decrease in the number of infections (Fig. 3). Prior to 2000, standard IFN was used, which had a lower SVR.

While the total number of infections is expected to decline in most countries, the number of cases with more advanced liver diseases is expected to increase (Table 3 and Figs 3 and 4). As the infected population ages, HCVinfected individuals will advance to cirrhosis, decompensated cirrhosis and hepatocellular carcinoma (HCC). As shown in Fig. 4, the number of HCC and decompensated cirrhosis is expected to increase across the board with the exception of France. France was a noted exception among the countries studied. It was estimated that 10 100 F2-F4 cases are treated in 2013 at an average SVR rate of 60%. If the current treatment rate and efficacy continued in the future, the patient pool advancing to HCC and decompensated cirrhosis would be depleted. In other countries (Austria, Egypt, Germany and Sweden), the number of HCC and decompensated cirrhotic individuals will peak before 2030. This is due to the age of the infected population (Egypt), where mortality overtakes disease progression or is the result of a high treatment rate that prevents progression of patients (Austria, Germany and Sweden). Austria represents a special case, where a high number of liver transplants in the HCV-infected population leads to similar numbers of decompensated cirrhotic and HCC cases (Fig. 4).

There were a number of limitations that could impact the outcomes from this study. The model used the annual number of new cases and tracked their progression over time. As described earlier, distribution of new cases from 1950 to the year of available data was back-calculated using relative incidence and allocation of the new cases by age and gender. This methodology was surprisingly robust. The combination of known prevalence and the corresponding age and gender distribution provided a very limited number of solutions that could match published data. In addition, if there were two HCV prevalence estimates, it was possible to estimate the number of new infections required to match the observed decline or increase [85]. The end result was an estimated number of HCV infections in a given year that matched published data [4] both in terms of total cases and the age/gender distribution. However, it was more difficult to estimate the number of new infections after the year of known prevalence. In every country, an analysis of the key risk factors was used to estimate the more recent number of new infections. Factors considered were new HCV infection among IDU, continued nosocomial infection and impact of immigration on the new cases of HCV. A linear trend was used to forecast future annual number of new cases. However, published data [87] show an erratic number of new infections among IDU. A limitation of this study is the assumption that the number of new cases will remain constant or linear after 2013. Higher number of new infections could result in higher total number of infections in 2030.

An analysis was conducted to identify the annual number of new cases to keep the total number of HCV infections constant in 2013 and 2030. The results are shown in Table 4. In some countries (Australia, Czech Republic and Sweden), very little or no increase in new cases is required to keep the total number of infections constant. In other countries, the annual number of infections has to more than double to see a flat number of HCV infections.

A further limitation of this analysis is the assumption that sufficient numbers of diagnosed patients will be available for treatment. In reality, as the diagnosis rate increases, it will become more difficult to find undiagnosed patients. In addition, diagnosed patients may not have easy access to care. Thus, the ability of a country to treat its HCV population may be limited by the number of available diagnosed eligible patients.

In addition, the model does not consider the progression of cured HCV patients. Studies have shown that more advanced patients may continue their disease progression after achieving SVR, although at a slower rate [5]. The data presented here may overestimate the reduction in HCC and decompensated cirrhosis cases, as the scope of the analysis was limited to HCV viremic individuals. Another element not addressed by this model is potential contribution of extrahepatic manifestations of HCV infection on all-cause mortality.

In conclusion, this study demonstrated that the total number of HCV infections is projected to decline in nearly every country studied due to a reduction in risk factors for new infections (e.g. screening of blood supply), aging of the infected population and the corresponding increase in mortality, and treatment of infected individuals. However, even though the total number of infected individuals is expected to decline, those who remain infected are expected to progress to more advanced stages of liver disease, and thus a sharp increase in HCC, liver-related deaths, decompensated cirrhosis and cirrhosis cases are expected. Thus, the HCV disease burden will not be controlled by the current treatment paradigm. Increased treatment and/or higher efficacy therapies are needed to keep the number of HCV individuals with advanced liver diseases and liver-related deaths from increasing. This suggests that strategies are required to manage the expected increase in HCV disease burden.

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# DISCLOSURES

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